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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/880,821	06/15/2001	Peter Anthony Minter Eagles	1208-49	6603

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EXAMINER
ZARA, JANE J

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 12/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/880,821	EAGLES ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14 and 17-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14 and 17-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This Office action is in response to the communication filed 9-10-03.

Claims 1-10, 12-14, 17-21 are pending in the instant application.

Response to Arguments and Amendment

Withdrawn Rejections

Any objections or rejections not repeated in this Office action are hereby withdrawn.

New Rejections and Rejections Necessitated by Amendments

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-10, 12-14, 17-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-10, 12-14 and 17-21 are vague and indefinite for containing the language indicated below.

In claim 1, lines 4-7, the language "will cleave" is vague and unclear regarding its description of the ribozyme (e.g. does this future tense mean that the ribozyme construct is unable to cleave the substrate at the present time?) (Perhaps replacing "will cleave" in line 4 with -- cleaves--; and replacing "the target-cleaving ribozymal DNA sequence, when transcribed to RNA, cleaving a target RNA sequence present in CCR5

or CXCR4 RNA, and which contains a first recognition sequence (5' to 3'):" with -- wherein said target-cleaving ribozymal DNA sequence comprises a first recognition sequence (5' to 3') complementary to CCR5 or CXCR4 mRNA:-- would be remedial).

In claims 2-10, line1, the use of the article "A" is improper because what it describes lacks proper antecedent basis (e.g. perhaps replacing "A" with -- The --would be remedial).

In claim 6, lines 2 and 3, it is unclear how a promoter may further comprise an IRES. IRES are placed in polycistronic vectors between discrete translatable entities, and do not exist in promoters.

In claim 7, line 4, the term "representable form" is vague and unclear (e.g. Does this mean that there other forms that represent the claimed construct?) (e.g. perhaps replacing "a representable form" with -- forms --would be remedial).

In claim 8, lines 1 and 2, "first and second structure-stabilising stem loops" lacks proper antecedent basis.

In claim 10, lines 3-8, the use of the article "A" is improper because what it describes lacks proper antecedent basis (e.g. perhaps replacing "a" with – the – would be remedial).

In claim 17, line 6, the term "a form represented" is vague and unclear (e.g. Does this mean that there other forms that represent the claimed construct?) (e.g. perhaps replacing "a form represented" with – forms – would be remedial); in line 7, replacing "steps" with – stems—would be remedial; in line 10, replacing "cleaving" with – cleaves—would be remedial; in line 11, the term "which" renders the claim vague and

unclear because it is unclear what "which" is referring to (e.g. perhaps replacing ""which" with –wherein said target cleaving ribozymal DNA sequence comprises—would be remedial).

In claim 18, line 1, "Ribozymal" without a proper article lacks proper antecedent basis (e.g. perhaps replacing "Ribozymal" with –a ribozymal—would be remedial; replacing "will cleave" with –cleaves—would be remedial).

In claim 19, line 1, "Ribozymal" without a proper article lacks proper antecedent basis (e.g. perhaps replacing "Ribozymal" with The ribozymal—would be remedial); in lines 1 and 2, the metes and bounds of "tandem CCR5 RNA and CXCR4 RNA-cleaving sequences" cannot be determined.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3 and 4 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a vector system comprising a first and second vector, which first vector comprises a first promoter operably linked to a gene which is expressible to produce an activator protein capable of acting on a second promoter.

The specification and claims do not indicate what distinguishing attributes are concisely shared by the members of the broad genus comprising an activator protein capable of acting on a second promoter. The scope of the claims includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members if permitted. No common structural attributes identify the members of the this broad genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics concisely identifying members of the proposed, and because the genus is highly variant, the description provided is insufficient. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to adequately describe the genus drawn to activator proteins capable of acting on a second promoter. Thus, Applicant was not in possession of the claimed genus.

Claims 12-14, 20 and 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions and methods for the in vitro inhibition of expression of CCR5 and CXCR4, does not reasonably provide enablement for compositions and methods of treating HIV infection in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to compositions and methods for the treatment of HIV infection in a human comprising the administration of vectors comprising ribozymal DNA that specifically targets and cleaves mRNA encoding CCR5 and/or CXCR4.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate the state of the art of antisense (and hence ribozyme) treatment in organisms. Branch and Crooke teach that the in vivo (whole organism) application of nucleic acids (such as antisense) is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of *in vivo* inhibition of target genes. (See entire text for Branch and especially pages 34-36 for Crooke). The high level of unpredictability regarding the prediction of antisense efficacy in treating disease states was illustrated in the clinical trial results obtained by ISIS pharmaceuticals for the treatment of Crohn's disease using antisense targeting ICAM-1, whereby the placebo treatment was found more successful than antisense treatment (BioWorld Today: See entire article, especially paragraphs 3 and 5-7 on page 1). Additionally, Palu et al teach that the success of gene delivery using virally derived vectors is dependent on the empirical determination of successful gene transduction for a given vector and a given target cell (See entire article, especially page 4, section 2).

Tamm et al, in a review article discussing the therapeutic potential of antisense in treating various forms of neoplasia, conclude that "Proof of clinical efficacy, of any of the antisense oligonucleotides in the field of oncology, is still missing." (see especially pages 490-493 for a summary of various clinical trials in process using antisense). Additionally, Agrawal et al point to various factors contributing to the unpredictability of antisense therapy, including non-antisense effects attributed to secondary structure and charge, as well as biological effects exerted by sequence motifs existing within the antisense or ribozyme sequences, all providing for unpredictable in vivo side effects and limited efficacy (e.g. see pages 72-76). Agrawal et al speak to the unpredictable nature of the antisense field thus: "It is therefore appropriate to study each antisense oligonucleotide in its own context, and relevant cell line, without generalizing the results for every oligonucleotide." (see page 80).

Cellular uptake of vectors encoding antisense or ribozymes by appropriate target cells is another rate limiting step that has yet to be overcome in achieving predictable clinical efficacy using antisense. Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of nucleic acids in vitro and in vivo (see Agrawal et al especially at pages 79-80; see Chirila et al in its entirety, especially pages 326-327 for a general review of the "important and inordinately difficult challenge" of the delivery of therapeutic antisense to target cells).

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of inhibiting CCR5 or CXCR4 in vivo, nor of treating

human for HIV using the nucleic acid constructs claimed. The specification teaches the in vitro targeting and inhibition of expression of CCR5 or CXCR4 using the nucleic acid constructs claimed. The specification fails to teach the successful targeting and inhibition of CCR5 or CXCR4 in an organism, comprising the administration of the vectors claimed, nor the treatment of HIV infection in a human comprising the administration of the nucleic acid constructs claimed. One skilled in the art would not accept on its face the examples given in the specification of the in vitro targeting and inhibition of expression of CCR5 or CXCR4 as being correlative or representative of the in vivo targeting and inhibition of CCR5 or CXCR4, or the treatment of HIV infection, in view of the lack of guidance in the specification and known unpredictability associated with the ability to predict the in vivo effects of nucleic acids encoding ribozymes in treating HIV in an organism. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with in vivo delivery and treatment effects provided by nucleic acids administered, and specifically regarding the instant compositions and methods claimed.

The breadth of the claims and the quantity of experimentation required. The claims are drawn to compositions and methods for the treatment of HIV infection in a human comprising the administration of vectors comprising ribozymal DNA that specifically targets and cleaves mRNA encoding CCR5 and/or CXCR4. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites, modes of delivery and formulations to target appropriate cells and /or tissues harboring the target genes CCR5 or CXCR4, whereby

their expression is inhibited in vivo, and further whereby treatment effects are provided for HIV infection in an organism. Since the specification fails to provide any particular guidance for the successful in vivo inhibition of expression of CCR5 or CXCR4 comprising the administration of the vectors claimed, and fails to provide guidance for the successful treatment of HIV in an organism comprising the administration of vectors claimed, and since determination of these factors is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(703) 306-5820.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. Any inquiry regarding

this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (703) 305-3413. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER

JZ
December 1, 2003